REMARKS

Claims 1-12, 17, 18, and 21-45 exist upon entry of the above amendment. Claims 13-16 and 19-20 have been cancelled without prejudice. Claims 1-12, and 17 have bee amended without prejudice.

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I Claims 1-11, 13, 16 and 18-20, as drawn to compounds of formula I, pharmaceutical compositions and method of use of formula (I) wherein ring B represents benzodiazepin-2-one (see examples 1-8 and 10-15);

Group II. Claims 1-12 and 17-20, drawn to compounds of formula I, pharmaceutical compositions and method of use of formula (I) wherein ring B represents dibenzoazepinone (see example 9); and

Group III. Claims 1-20, drawn to compounds, pharmaceutical compositions and method of use of formula (I) not falling under groups I and II above, but generically embraced by the claims, *i.e.*, wherein ring B is NOT the dibenzoazepinone or benzodiazepinone core.

According to the Examiner, Groups I-III are drawn to structurally dissimilar compounds, made and used independently and independent and patentably distinct. Examiner's restriction has been made final. As requested, Applicant elects to prosecute the invention of group II, claims 1-20, reading on compounds, compositions and methods of use of compounds wherein ring "B"

represents dibenzoazepinone. However, Applicant reserves the right to prosecute presently excluded or non-elected subject matter in separate divisional applications. Claims 13-16 along with subject matter not falling under elected group II is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

No amendment of inventorship is deemed necessary upon the cancellation of claims to a non-elected invention.

Improper Markush Rejection

Claims 1-11 and 18-20 are rejected as being drawn to an improper Markush group. Applicant has amended the Claims consistent with the Examiner's description of the class of compounds for Group II. Thus, it is submitted that the rejection has been overcome.

Claim Rejections -35 USC 112, Second Paragraph.

Claims 1-11 and 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(i). Applicant has amended the Claims 1-12 and 17 deleting the term 'prodrug'. Claims 19-20 have been cancelled without prejudice. Contrary to the Examiner's allegation, claim 1 includes 'or a pharmaceutically acceptable salt'.

(ii) The allegedly indefinite terms "cycloalkyl" and "carbocycle" are found fully defined in the instant Specification under 'Definitions' on page 74, paragraphs 156 and 157. Therefore,

these rejections are now deemed moot.

(iii) The group heterocycle is defined in the instant Specification, page 74, paragraph 158, as to ring saturation, number of rings and heteroatoms; moreover, numerous examples are provided: "5 to 10 membered heterocycle" (paragraph 158).

(iv) The group C_6-C_{10} aryl has been amended deleting C_6-C_{10}. The term aryl is described on page 75, paragraph 160 of the instant Specification.

(v) Claim 19 has been cancelled without prejudice.

(vi) Claim 20 has been cancelled without prejudice.

(vii) Claim 11 has been amended to remedy an inadvertent computer glitch resulting in empty boxes. X is as shown on page 65 , paragraph 104 of the Specification.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to the invention. The specification is not adequately enabling for the scope of the compounds claimed. The only compound made is that of claim 17. This does not give a reasonable assurance that all, or substantially all of the compounds that could be made are useful. The claims are not drawn in terms of a recognized genus but are directed to a more or less artificial selection of compounds.

There is no reason why a claim drawn in this way should not be limited to those compounds which are shown to be useful. An Applicant is not entitled to a claim for a large group of compounds merely on the basis of a showing that a single compound is useful and a general suggestion of a similar utility in the others.

Rejection under 35 USC 112, First Paragraph

In view of the alleged indefiniteness of the term "neurological disorders, Claims 19 and 20 have been cancelled without prejudice and entered the new claims 33-45 limiting the scope of "neurological disorder" to Alzheimer's disease. In traverse of the rejection, Applicant asserts that these new added Claims are enabled by the instant description.

Applicant submits that for enablement, in vitro assays and in vivo models for determining β-amyloid production are enough, human models of clinical efficacy are not required.

Furthermore, to be art recognized, Applicant submits there is no requirement for the mechanism to be proven in human, again in vitro assays and in vivo models are sufficient. Lastly, where recognition in the art is minimal, then enablement becomes an issue of predictability. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. MPEP 2164.03. Therefore, Applicant needs only establish predictability to satisfy enablement for the scope of treatment disclosed in the Specification that Alzheimer's Disease (AD) is a progressive neurodegenerative disorder which leads to profound dementia and death. The brains of AD victims are characterized by extracellular amyloid plaques. The principal component of plaques is a fibrillar form of a 40 to 42 amino acid amyloid-β peptide (Aβ). Recognition in the art, supported by disease genetics, cell biology and animal models, that amyloid-β peptide plays a causative role for in Alzheimer's Disease, known as the amyloid hypothesis, is now widely accepted. See 1) Dingwall; J. Clinical Invest., 108, Nov. 2001, 1243-1246; 2) Selkoe; J. Alzheimer's Disease, 3, 2001, p 75-81; 3) Tanzi and Parson, "Decoding Darkness, The Search for the Genetic Causes of Alzheimer's Disease", Perseus Publishing, 2000, pages xvii - xviii; 4)

Olson et al., Current Opinion in Drug Discovery and Development, 4, 2001, p 390-401. Selkoe, especially, discusses thirteen points which support the Aβ hypothesis of AD.

As discussed by Applicant in the instant Specification, the source of the Aβ peptide is a protein known as APP, which is processed by enzymes known as β- and γ-secretases. A particularly compelling piece of evidence for the amyloid hypothesis is that AD-associated mutations in APP near the β- and γ-secretase cleavage sites of APP lead to early onset forms of AD. When APP proteins having these mutations are expressed in cells and animals, increased blood levels of the more fibrillar form of Aβ are secreted. As previously stated, Aβ is the principal component of extracellular amyloid plaques found in the brains of AD victims.

Applicant has provided assays to assess the inhibitory activity of the compounds of the invention against production of Aβ. Wagner et al. (J. Clinical Invest. Nov. 1999, 104, 1329-1332) state that there are animal models which "provide excellent tools for examining not only potential drugs, but also genetic and environmental modifiers of [Alzheimer's Disease]." As such, Applicant has disclosed *in vitro* methods for determining β-amyloid production and *in vivo* transgenic mouse models are available to one skilled in the art to permit studies of human APP proteolysis, Aβ deposition, or neuritic plaque formation. Applicants submit that one skilled in the art would not doubt the usefulness of the present invention. On the contrary, Dingell states on page 1246 last paragraph that behavioral deficits in APP transgenic animals correlates closely with Aβ blood levels and that the secretases remain the most promising targets for treatment of Alzheimer's Disease.

Thus, Applicant submits that the instant mechanism is art recognized and that the invention is enabled for the scope of treatment of Alzheimer's Disease. Therefore, Applicant, respectfully, submits that the rejection under 35 USC 112 is improper and requests that the

rejection be withdrawn.

OBJECTIONS

Claim 17 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicant traverses the objection in view of the present amendment of the main claim and the intervening claims, thus rendering the antecedent claims and claim 17 allowable.

CONCLUDING REMARKS, REQUESTS AND FEE PAYMENTS

For all of the reasons set forth above, it is firmly believed that pending claims 1-12, 17, 18, and 21-45 are allowable. Early notification of allowance is solicited.

Fees

The Commissioner is hereby authorized to charge payment of any fees that may be required under 37 C.F.R. §1.16 in connection with the paper transmitted herewith, to Deposit Account No. 03-3975.

Respectfully submitted,

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